Hendrickson, S. A., Donovan, R., Harries, L., Wright, T., Whitehouse, M. R., & Khan, U. (2020). Time to Intravenous antibiotic Administration (TIbiA) in severe open tibial fractures: impact of change to national guidance. *Injury*. https://doi.org/10.1016/j.injury.2020.03.005

Title

Time to Intravenous antibiotic Administration (TIbiA) in severe open tibial fractures: impact of change to national guidance

Authors

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Keywords

Open Fracture; Tibia; Major Trauma; BOAST; Infection; Orthoplastic

Abstract

Introduction

Severe open tibial fractures are limb-threatening injuries. Outcomes depend on a complex interplay of patient, injury and treatment factors. 2009 guidelines from the British Orthopaedic Association (BOA) and British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) recommend prophylactic intravenous antibiotic administration within three hours of injury. More recent National Institute for Health and Care Excellence (NICE) 2016 guidelines recommend pre-hospital antibiotic administration where possible. This study aimed to analyse the impact of time to antibiotics on development of deep infection.

Methods

Adult acute Gustilo-Anderson 3B open tibial fractures managed at a single UK Major Trauma Centre were reviewed retrospectively over a three-year period, including a period before and after the regional ambulance service introduced a policy of administering pre-hospital intravenous antibiotics to open fractures in 2016. Development of deep infection was recorded as the primary outcome measure. Complete case regression analysis was performed. Time was assessed as a continuous variable and as thresholds with antibiotics received within one or three hours of injury.

Results

156 patients with 159 fractures were included. Following introduction of new guidance in 2016, median time to antibiotics decreased from 180 to 160 minutes and more patients received pre-hospital antibiotics (2% vs. 33%). Overall, 7.5% developed deep infection (n=12) within a median follow-up of 26 months. Logistic regression found no relationship

between any independent variable, including time to antibiotic administration, and development of deep infection.

Conclusions

There are a variety of factors identified in the literature and in national policies and treatment guidelines as potentially modifiable to reduce the risk of deep infection following open fractures. In this study, time to antibiotic administration was not associated with the risk of developing deep infection. The results of this study demonstrate a low infection rate, which may be due to expedient expert care delivered by a dedicated orthoplastic service in line with national guidance where achievable.

Introduction

Severe open tibial fractures are limb-threatening injuries. Contemporary treatment strategies have drastically improved outcomes, meaning limb salvage is now not only possible, it is the standard of care. Despite this, reported deep infection rates vary widely: recent series report rates between 5 – 20%, even in specialist centres[1-5]. Deep infection can lead to hospital readmission, further surgery, and amputation, which can adversely affect rehabilitation and overall outcome and lead to an increased health economic burden[6].

The current 'gold standard' approach to such injuries involves a joint 'orthoplastic' approach with expedient antibiotic delivery, surgical wound excision, and definitive bony fixation and soft tissue coverage within the first few days following injury. National United Kingdom (UK) guidance issued jointly in 2009 by the British Orthopaedic Association (BOA) and British Association for Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) recommends prophylactic intravenous antibiotic administration within three hours of injury[7]. Updated guidance issued by the UK National Institute for Health and Care Excellence (NICE) in 2016 recommends antibiotic delivery within the first hour post injury (that is, pre-hospital) where possible, and the newest BOA Standard for Trauma on this topic (BOAST4) has been updated in accordance with this[8,9].

The evidence supporting an association between the timing of delivery of antibiotics with the risk of deep infection is mixed. Patzakis and Wilkins found infection rates were nearly twice as high in patients receiving antibiotics more than three hours post injury[3]. Lack and colleagues found deep infection was approximately three times more frequent if antibiotics were delivered between 60- and 90-minutes post injury compared to if they were delivered within 60 minutes[2]. However, a 2013 study found no difference in non-union or deep

infection rates in those patients receiving intravenous antibiotics by HEMS crews pre-hospital[10], and a recent systematic review found no robust evidence of an association, with all published studies being at high risk of bias, and recommended further evidence was established before policy changes were instigated[11].

Existing evidence is largely derived from small, heterogenous cohorts, making it difficult to draw meaningful conclusions to guide clinical practice. A number of the published studies are old and not reflective of contemporary practice. This study aimed to analyse the impact of time to antibiotics on development of deep infection in severe open tibial fractures managed in a specialist orthoplastic setting in the UK.

Methods

Adult acute Gustilo-Anderson 3B open tibial fractures managed between 2015 and 2018 at a single UK Major Trauma Centre were reviewed retrospectively. Patients undergoing initial emergency management at a district general hospital and transferred for definitive management to the Major Trauma Centre were included. Patients were followed up for a minimum of one year in line with the Getting it Right First Time definition of deep incisional infection in the presence of an implant[12]. These guidelines relate to infections in the elective setting, but have been used in the absence of an accepted minimum follow-up period in the trauma setting.

Excluded patients and corresponding exclusion criteria are listed in Figure 1.

Development of deep infection was recorded as the primary outcome measure. Deep infection was defined as clinical presentation with infected non-union of the tibia, delayed (partial) flap failure due to infection, deep infected collection requiring return to theatre, and/or removal of metalwork due to infection. All infections were confirmed by positive direct or enrichment culture of deep tissue samples.

The regional ambulance service introduced a policy enabling paramedics to administer pre-hospital intravenous antibiotics in 2016.

Statistical analyses were performed using GraphPad Prism (version 8.0.2, GraphPad Software Inc., San Diego, USA). Continuous data was checked for normality with a D'Agostino and Pearson test. None of the data was normally distributed and therefore central tendency was described with the median and interquartile range.

A complete case multiple regression analysis was conducted to determine which factors influenced the risk of deep infection (dependent variable). Seven cases were excluded from the analysis due to missing data (see Fig. 1). Independent variables included in the final multiple regression model were gender, age, follow-up time (months), primary or secondary transfer, ISS, unilateral or bilateral fracture, injury mechanism causing gross contamination (i.e. marine-, farmyard- or sewage-related injuries), presence of at least one relevant comorbidity (diabetes mellitus, peripheral vascular disease, current smoking status, and/or immunosuppression), type of antibiotic, time from injury to first antibiotic dose, time from injury to first debridement and time from injury to definitive coverage. Time was assessed as a continuous variable and as thresholds with antibiotics received within one or three hours of injury.

Multicollinearity was assessed and addressed where it was a problem (R^2>0.75); it was addressed either by grouping variables or removal of variables from the model (e.g. type of antibiotic) until it was no longer a problem.

Results

159 grade 3B open fractures in 156 patients between October 2015 and June 2018 met the inclusion criteria (Fig. 1). The male:female ratio was 1.2:1. The median age at injury was 51 years (interquartile range (IQR) 31 to 71). The median follow-up was 26 months (IQR 18 to 39). The majority of patients (n=93, 60%) were primary transfers from the site of injury to the Major Trauma Centre (MTC); the remainder were received at peripheral trauma units and transferred to the MTC within 48 hours. Some underwent initial surgical wound excision and temporary stabilisation at the referring trauma unit. The median ISS was 9 (IQR 9 to 9, minimum 4, maximum 57).

The median time to the first dose of antibiotic post injury was 162 minutes (IQR 120 to 207). Overall, 21% of patients (n=33) received antibiotics prehospital. Forty-five percent (n=72) received co-amoxiclav, especially those receiving antibiotics pre-hospital and those transferred in from district general hospitals. Thirty-five percent (n=56) received a combination of flucoxacillin and gentamicin, which is the recommended first line prophylaxis at the studied centre. The median time to first surgical wound excision was 19 hours (IQR 14 hours 19 minutes to 23 hours 40 minutes). The median time to definitive soft tissue coverage was 64 hours (IQR 40 hours 30 minutes to 87 hours 10 minutes).

Twelve deep infections as defined above (7.5% of fractures) were recorded (Table 1). The multiple regression model (Table 2) showed that whether a patient received their first dose of antibiotics prehospital (p=0.963), the time to delivery of the first dose of antibiotic (as a continuous variable) (p=0.431), whether antibiotics were delivered within one hour (p=0.099) or three hours (p=0.848) of injury, the time to first surgical wound excision (as a continuous variable) (p=0.182) and the time to definitive soft tissue coverage (p=0.414) were not associated with the development of deep infection.

Following introduction of new guidance in 2016, median time to antibiotics decreased from 180 to 160 minutes and more patients received pre-hospital antibiotics (2% vs. 33%). The infection rate decreased from 9.8% to 6.2%, but this was not statistically significant (p=0.538).

Discussion

This study found that within a specialist orthoplastic setting, where severe open tibial fractures are managed expediently by a dedicated service largely in accordance with national best practice, there was no correlation between timing of administration of intravenous antibiotics and deep infection, and, indeed, no other independent variable was found to be associated with the development of deep infection in this cohort of patients.

The number of patients receiving pre-hospital antibiotics did increase following introduction of new guidance and the infection rate did fall; however, this was not statistically significant.

Two thirds of patients (67%) did not receive pre-hospital antibiotics, indicating either that the guidelines proved difficult to comply with in our region or that it is taking time for the

change in policy to result in a change in practice. The reasons for this are not clear, but may relate to the study period falling within the early phase following introduction of new guidelines and the time needed to train healthcare personnel and provide resources to deliver the new treatment policy, particularly given the costs involved.

In a healthcare service operating with finite resources, national recommendations must focus on high impact interventions with a robust evidence base. The cost associated with training paramedics to recognise open fractures, administer intravenous antibiotics for this indication and providing paramedic crews to attend all patients with a possible diagnosis of an open fracture must be weighed against any potential return in gains in the form of reduced infection rate.

The clinical outcome in patients with severe open tibial fractures is influenced by a complex interplay between patient, injury and treatment factors. Many elements of care governed by national guidance are not supported by unequivocal clinical evidence: time to initial surgical debridement and wound excision has been shown by some studies to be associated with increased risk of deep infection[13] but others have shown no association[1,4]. Similarly, use of negative pressure wound therapy to temporise open fractures, which is recommended by national societies (BOA, BAPRAS) and routinely used by many specialist centres, has recently been shown to have no impact on long term outcome in a randomised controlled trial of open lower limb fractures[14].

Similarly, some studies support administration of antibiotics within one hour of injury[2], while others have shown that pre-hospital administration of antibiotics does not impact on deep infection or non-union rates[10]. A large, albeit heterogenous, Canadian cohort study found no

association between time to antibiotics and development of deep infection[15,16]. A recent systematic review on the topic did not find enough robust evidence to support administration of pre-hospital antibiotics[11], findings supported by the results of this paper.

It is difficult to glean meaningful conclusions to guide clinical practice from the available evidence as many studies are outdated or performed outside of the UK, where the treatment framework may significantly differ. However, the findings of the United States-based LEAP group, showing time to arrival at a specialist centre to be the only significant factor impacting on deep infection, seem at least logical given the complexity of these injuries. The infection rate reported here is lower than most other comparable studies, and this may be a result of expedient, high quality care delivered by pre-hospital and emergency practitioners and by a dedicated, expert joint orthoplastic service in accordance with national guidance where achievable.

Strengths and limitations

This is one of the largest UK cohorts of Gustilo-Anderson grade 3B open tibial fractures to be reported in the literature. However, it is a retrospective, single-centre study. The primary outcome measure, deep infection, is a relatively rare event in this cohort, making analysis by logistic regression difficult to interpret. No power calculations were undertaken *a priori*, but *post hoc* power calculations (achieved power of 0.9 from calculated effect size, assuming a two-tail test) suggest the sample size was large enough to detect a difference if one was present. The complex nature of these injuries and their management mean that randomised controlled trials are required to better guide clinical practice rather than further, larger observational studies. We propose a randomised controlled trial to compare the impact on

deep infection rates of immediate, pre-hospital administration of antibiotics (within one hour of injury) *vs.* the early, in-hospital administration of antibiotics (within three hours of injury).

Conclusion

There is no consensus in the existing literature as to which element of care impacts the most on development of deep infection in severe open tibial fractures, and therefore which element should be emphasised in national guidance and supported by prioritisation of funding and resources. Our centre has a low infection rate, which may be due to expedient, expert care delivered by a dedicated orthoplastic service in line with national guidance where achievable. The vital next step in better understanding these complex and life-changing injuries is to recruit patients to a large, prospective, national randomised controlled trial of severe open tibial fractures.

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Figure 1: Flow diagram of excluded patients

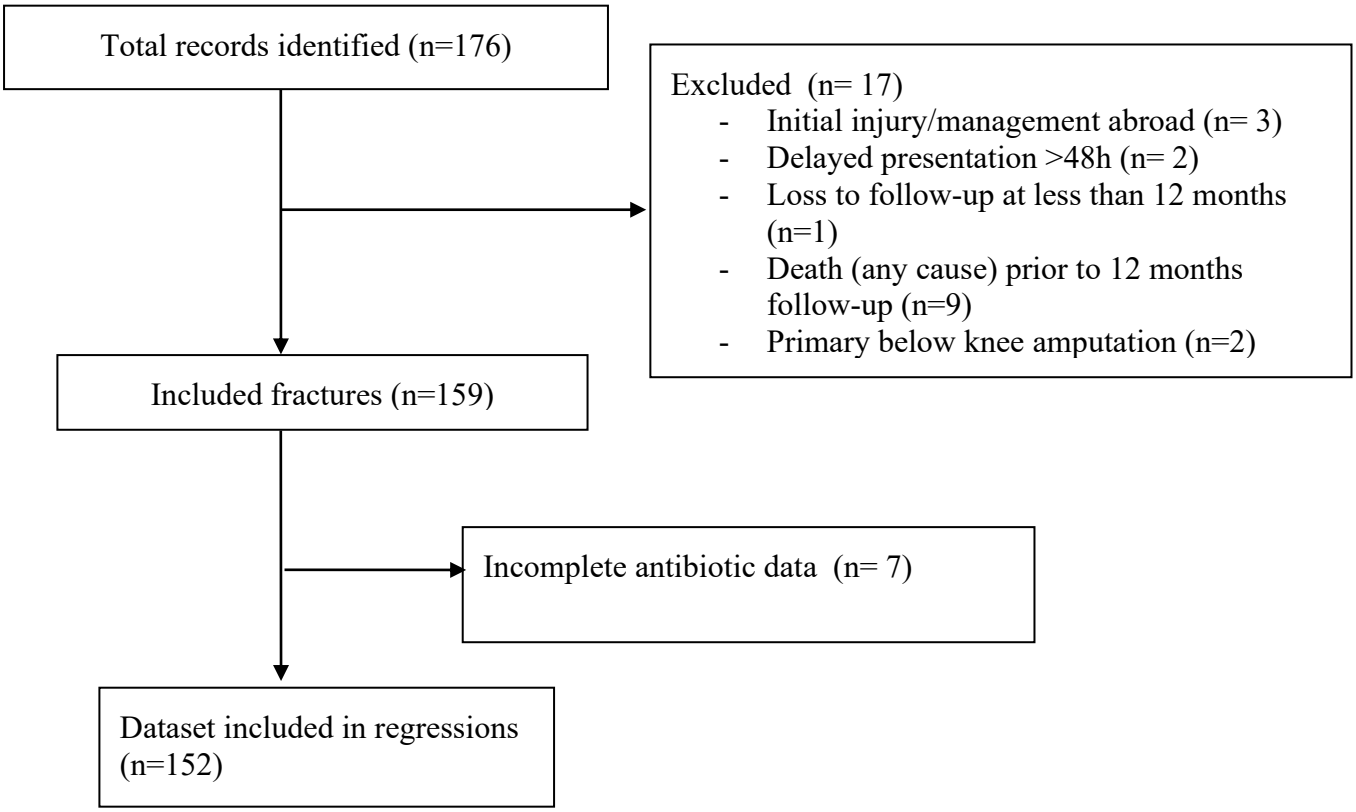

Table 1: Details of deep infections. (PMH, past medical history; MTC, Major Trauma Centre; DM, Diabetes Mellitus; PVD, peripheral vascular disease; ALT, anterolateral thigh; ROMW, removal of metalwork; BKA, below knee amputation; AKA, above knee amputation; Staph., staphylococcus; Strep., streptococcus; E., escherichia)

Age	**ISS**	**PMH**	**Primary/ secondary transfer to MTC?**	**Antibiotic given**	**Time to antibiotics (min)**	**Time to diagnosis of deep infection (weeks)**	**Initial reconstruction**	**Details of infection and subsequent management**	**Organism**
52	29	Smoker	Primary	Flucloxacillin + gentamicin	207	84	Free scapular/ parascapular flap	Infective non-union, ROMW	E. coli, Staph. capitis
27	10	Smoker	Secondary	Co-amoxiclav	60	13	Free ALT flap	Flap cellulitis, deep collection. Debridement, washout, ROMW	Staph. aureus
38	9	Smoker	Primary	Flucloxacillin + gentamicin	182	4	Direct closure	ROMW, 2-stage debridement, free ALT reconstruction	Beta haemolytic group G strep.
44	9	DM	Secondary	Gentamicin + teicoplanin	153	10	Local fasciocutaneous flap	2-stage debridement, exchange of metalwork	Staph. aureus, Enterobacter cloacae
38	13	None	Primary	Co-amoxiclav	155	14	Free scapular/ parascapular flap	2-stage debridement, ROMW, failed salvage free ALT flap, subsequent successful medial gastrocnemius flap with bone transport	Morganella morganii, Staph. capitis
21	9	None	Secondary	Co-amoxiclav	105	3	Free ALT flap	Exchange metalwork, medial gastrocnemius flap	Staph. epidermidis (on enrichment only)
52	9	IHD, HTN, RA	Primary	Flucloxacillin + gentamicin	250	54	Free ALT flap	Debridement, ROMW; subsequent infection revision metalwork with	Staph. aureus, Enterococcus faecalis

								osteomyelitis; BKA	
71	9	PVD, DM, smoker	Primary	Flucloxacillin + gentamicin	325	2	Local fasciocutaneous flap	BKA for deep wound infection	Strep. agalactiae, Staph. aureus, Staph. epidermidis
23	9	None	Primary	Gentamicin + teicoplanin	163	7	Free ALT flap	2-stage debridement, exchange metalwork	Lelliottia aminega, Staph. epidermidis
81	9	None	Primary	Co-amoxiclav	80	18	Medial + lateral gastrocnemius flap + peroneus brevis flap	AKA for osteomyelitis	No deep samples sent but frank pus seen intra-operatively
29	25	None	Secondary	Co-amoxiclav	385	19	Medial gastrocnemius flap	Deep collection requiring washout; ROMW	Staph. aureus
52	9	None	Primary	Co-amoxiclav	74	33	Free ALT flap	Debridement, sampling, ROMW, transfer to BRI for frame	Staph. aureus

Table 2: Multiple regression model investigating factors that significantly predict deep infection.

Variable	Multiple regression model estimate	95% confidence interval	t value	p value
Gender	-0.0610	-0.1708 to 0.0487	1.100	0.273
Age	-0.0007	-0.0034 to 0.0019	0.536	0.593
Follow up (months)	0.0021	-0.0028 to 0.0071	0.848	0.398
Primary or secondary transfer	-0.0671	-0.1721 to 0.0379	1.264	0.209
ISS	0.0005	-0.0059 to 0.0070	0.168	0.867
Diabetes	0.1430	-0.0583 to 0.3443	1.406	0.162
PVD	-0.0495	-0.2366 to 0.1375	0.524	0.601
Smoker	0.0226	-0.1040 to 0.1492	0.353	0.725
Immunocompromise	-0.0110	-0.1355 to 0.1138	0.172	0.864
Unilateral or bilateral fracture	-0.0468	-0.2881 to 0.1946	0.383	0.702
Contamination with marine, farmyard or sewage waste	-0.0728	-0.4814 to 0.3358	0.353	0.725
Antibiotic received pre-hospital	-0.0036	-0.1547 to 0.1476	0.047	0.963
Time from injury to first dose of antibiotic	-0.0003	-0.0010 to 0.0004	0.791	0.431
Time from injury to first debridement	0.0047	-0.0022 to 0.0117	1.343	0.182
Time from injury to definitive coverage	-0.0004	-0.0015 to 0.0006	0.819	0.414
Antibiotics received within 1 hour of injury	0.1906	-0.0363 to 0.4175	1.663	0.099
Antibiotics received within 3 hours of injury	-0.0105	-0.1188 to 0.0978	0.192	0.848